REMARKS

Claims 33-53 were pending in the subject application. The specification has been amended to insert the language of original claims 1 and 2 into the Summary of the Invention. Support for this amendment is found in the specification as originally filed at page 42, lines 1-8. Claims 33-53 have been canceled without prejudice and new claims 54-71 have been added to more particularly describe what Applicants regard as the invention. The support for the new claims in the Specification and claims as originally filed is given in the Table below. The Table also shows the previously pending claim(s) to which each new claim generally corresponds, if any.

New Claim	Corresponding Previous Claim No.	Support in Specification and claims as originally filed
54. A method of inhibiting rejection of grafted cells, tissue, or organ in a mammal in need thereof	33, 45	Page 10, lines 26-29 Page 11, lines 25-30 Page 36, lines 31-34 (in need thereof)
comprising administering to the mammal a dose, effective to inhibit graft rejection,		Page 11, lines 20-23 Page 31 line 17 to page 32 line 3
of a composition comprising purified complexes, each complex consisting essentially of a heat shock protein non-covalently bound to a peptide,		Page 1, lines 19-21 Page 9, lines 15-21 Page 12, lines 5-8 Page 13, lines 21-22 Page 33, lines 6-10
wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ,		Page 9, line 36 to page 10 line 2
wherein the heat shock protein is a member of the hsp90 family of heat shock proteins, and		Page 8, lines 7-10 and lines 20-22
wherein the composition is administered after the cells, tissue, or organ is grafted.		Page 4, lines 23-25 Page 36, lines 26-27
55. . . . the method further comprising administering to the mammal a sample of cells or tissue obtained from the cell, tissue, or organ donor prior to administration of the heat shock protein.	33, 49	Page 4, lines 25-28 Page 37, lines 13-35 Page 38, lines 1-4
56. . . . wherein the amount of the complex present in the composition is 100 μg or more.	47	Page 31, line 16 to page 32 line 3

57. . . . wherein the complexes are isolated from a healthy organ of the mammal, wherein said mammal is not experiencing graft rejection or an autoimmune response directed at said healthy organ	50	Page 10, lines 4-8
58 wherein the heat shock protein is not an alloantigen of the grafted cells, tissue, or organ	35	Page 9, lines 34-36
59 wherein the grafted cells, tissue, or organ is skin, liver, kidney, heart, bone marrow, pancreas, lung, cornea, cartilage, or cells derived therefrom	36	Page 11, lines 25-30
60 wherein the grafted cells or tissue is skin or cells derived from skin	37	Page 11, lines 25-30
61 wherein the heat shock protein is a mammalian heat shock protein	38	Page 7, line 24
62 wherein the heat shock protein is human heat shock protein	39	Page 7, lines 24-26
63 wherein the heat shock protein is gp96	40	Page 7, lines 21-23
64 wherein the heat shock protein is hsp90	41	Page 7, lines 21-23
65 wherein the heat shock proteins of said complexes are a combination of gp96 and hsp90		Page 7, lines 21-23
66 method of claim 54, 55, or 56, wherein the mammal is human	43	Page 10, lines 26-29
67 method of claim 58, wherein the mammal is human	53	Page 10, lines 26-29
68 method of claim 63, wherein the mammal is human	52	Page 10, lines 26-29
69 wherein said composition comprises a purified population of complexes, each complex in said population consisting essentially of a heat shock protein non-covalently bound to a peptide, and wherein said population of complexes comprises different peptides	51	Page 12, lines 28-30 Page 13, lines 30-34 Page 9, lines 27-31
70 wherein the heat shock protein is gp96		Page 7, lines 21-23
71 wherein the mammal is human		Page 10, lines 26-29

Drawings

The Examiner stated that the Drawings filed September 26, 2005 were not acceptable because the changes to the drawings have not been identified and therefore the drawings have not been entered.

In response, Applicants identify the following changes in the Drawings as submitted in their Response Under 37 C.F.R. § 1.111 filed on September 26, 2005 compared to the drawings as originally filed with the application on September 10, 1999. First, each new drawing sheet contains a label at the top of the sheet identifying it as a "REPLACEMENT" sheet and identifying the Docket No., Serial No., Inventor names, and Title of the application. No such labels were present on the Drawings as originally filed.

As originally filed, drawing sheet 1 (Fig. 1) depicted 6 panels labeled as Postoperative Day 4, 5, 7, 8, 9, and 10, respectively. Each panel was labeled above the top row and beside the left column. Some of the panels also contained hand-written annotations. In the replacement sheets for Figure 1, each panel has been enlarged, placed on a separate sheet, and designated a lettered subfigure. Thus, original Fig. 1 is now represented on six separate sheets as Fig. 1A-1F. The typeface of the text labeling each panel on the top and left side has been changed and the text enlarged. In addition, the word "Donor" was added to the label at rows 3, 4, and 5 in each panel to clarify the source of the gp96 obtained from skin in those animals. A legend was added to the bottom of each of the replacement sheets for Figures 1A-1F. Finally, all hand-written annotations were removed from the replacement sheets for Figures 1A-1F.

As originally filed, drawing sheet 2 (Fig. 2) depicted 5 panels, labeled as Day 8, Day 12, Day 14, Day 16, and Day 19, respectively. The original drawing of Fig. 2 also contained hand-written annotations and a legend at the bottom of the sheet. In the replacement sheets for Figure 2, each panel of the original sheet 2 has been enlarged, placed on a separate sheet, and designated a lettered subfigure. Thus, original Fig. 2 is now represented on 5 separate sheets as Fig. 2A through Fig. 2E. The hand-written annotations have each been deleted or replaced with text in a different typeface and a new legend, both of which appear on each of the 5 replacement sheets. The abbreviations "ID" and "SC" have been written out as "administered intradermally" or "administered subcutaneously," respectively.

The originally filed drawings labeled Figure 3A, 3B, 4A, 4B, 5A, 5B, 6A, 6B, 7A, and 7B contained panels annotated by hand and abbreviated the words "subcutaneously" and

"intradermally" as "SC" and "ID" where those routes of administration were used. In the corresponding replacement sheets of Drawings, the panels have been enlarged and the hand-written annotations have either been deleted or replaced by text in new typeface and a new legend. The abbreviations "SC" and "ID" were replaced by "administered subcutaneously" or "administered intradermally", respectively. In some instances, the depiction of the graft in the panel has been simplified to convey the information in the handwritten annotations more clearly. For example, in Fig. 4A and Fig. 5A, where surrounding skin was visible and the grafts had fallen off, with the underlying wound visible, this result is depicted in the new figures as a dot inside an otherwise blank oval. In some figures, such as Fig. 3B, empty ovals were removed.

Applicants submit that the above-identified changes to the Drawings do not constitute new matter. In view of the foregoing, Applicants respectfully request that the Examiner accept and enter the Drawings in the file of this application.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement, Should be Withdrawn

The Examiner rejected claims 33-53 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the relevant art to make and/or use the claimed invention.

In response, Applicants note that claims 33-53 have been canceled. Applicants submit that new independent claims 54 and 55 satisfy the enablement requirements of 35 U.S.C. §112, first paragraph, for the following reasons.

First, Applicants note that new claims 54 and 55 each recite a method of inhibiting rejection of a graft *in a mammal in need thereof* comprising administering to the mammal *a dose, effective to inhibit graft rejection,* of a composition comprising purified complexes, each complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, and wherein *the heat shock protein is a member of the hsp90 family* of heat shock proteins.

Claim 54 further specifies that the composition is administered *after* the cells, tissue, or organ is grafted.

Claim 55 further specifies that the method comprises administering to the mammal a sample of cells or tissue obtained from the cells, tissue, or organ donor prior to administration

of the composition, and wherein said composition is administered prior to the cells, tissue, or organ being grafted to the mammal.

Applicants address the Examiner's concerns stated in the Final Office Action with respect to the new independent claims 54 and 55. First, with respect to the Examiner's rejections as they relate to the use of HSP70 family proteins in the claimed methods, Applicants note that the claims no longer recite HSP70 family proteins, rendering these rejections moot. Applicants address the remaining issues raised by the Examiner as follows.

Enablement: effective dose

The Examiner contends that the disclosure in the specification regarding the dose of hsp to be administered lacks sufficient detail to be enabling in view of the knowledge that some doses of hsp could be detrimental, *i.e.*, by stimulating the immune response against the graft, rather than inhibiting it (see pages 4-5 of the Office Action).

In response, Applicants submit that it is within the routine skill in the art to establish effective dosages for inhibiting graft rejection, even where it is known that some doses may be toxic or detrimental. In fact, finding the doses that optimize efficacy over toxicity generally is the goal of pre-clinical and early phase clinical testing for any pharmaceutical compound. Moreover, Applicants' disclosure guides the skilled artisan to start with a somewhat narrow range of effective doses, *e.g.*, in the 100-200 microgram or more range (see the specification at page 31, line 30 to page 32 line 3). The fact that broader dosage ranges are disclosed in the specification, and that some of the doses falling within those broad ranges may not be effective doses, does not render the experimentation required to arrive at the effective dosages undue, nor has the Examiner come forward with an explanation as to why, for example, determining a dose-response curve would entail undue experimentation. Applicants further note that the independent claims now specify the use of a dose "effective to inhibit graft rejection" and that dependent claim 56 recites that the amount of the complex in the composition is 100 micrograms or more.

Enablement: use of any HSP90 family heat shock protein

The Examiner acknowledges the statements by the Inventor, Pramod Srivastava, submitted in the Declaration accompanying Applicants August 25, 2004 response. At paragraph 15 of that Declaration, Dr. Srivastava explained why it was reasonable to expect that other members of the HSP90 family of heat shock proteins would exhibit the same immunosuppressive activity as Dr. Srivastava had demonstrated for gp96. Specifically, Dr.

Srivastava noted the high degree of structural homology among the members of the HSP90 family and stated that such structural homology lends itself to a reasonable expectation that an activity identified for a given HSP90 protein, such as gp96, would be shared by other members of the same family.

Nevertheless, the Examiner stated that "the Inventor's opinion alone is not persuasive" and that "sound scientific reasoning" is required to support the Inventor's assertions (see page 5 of the Office Action). In response, Applicants submit that the Inventor provided the scientific basis for his assertion, namely that given the high structural homology among HSP90 family proteins, it is reasonable to expect that members of the HSP90 family share the same activities. Thus, when one activity, such as immunosuppression, has been identified in a family member, it is reasonable to expect that other family members will also demonstrate that activity. Protein classification is essentially based on the fundamental assumption that high structural homology is at least a reliable predictor of similar function.

Enablement: use of hsp from any tissue source

The Examiner asserts that certain data in the specification and Chandawarkar *et al.* (1999) ("the 1999 paper") teach, contrary to Applicants' position, that the tissue source of the hsp is in fact important with respect to its immunosuppressive activity. Applicants do not dispute that the 1999 paper concluded that the immunosuppressive activity of gp96 was source-dependent, on the basis of a particular experiment described at page 1439 of that paper. However, the Examiner improperly dismisses the later teaching by the same group in Chandawarkar *et al.* (2004) ("the 2004 paper") that this conclusion was in error and that the immunosuppressive activity of gp96 is source-independent (see page 616, col. 2, para. 4 of the 2004 paper). The 2004 paper demonstrates that gp96 derived from both Meth A tumor cells and from liver exhibited immunosuppressive activity in the Meth A tumor model (see page 616, col. 2, para. 3) and concludes that "the suppression elicited by high-dose gp96 does not require source specificity" (see page 619, col. 2, para. 5).

A more recent paper by Chandawarkar *et al.* concludes that the tissue source of gp96 is not relevant to its immunosuppressive activity (see Kovalchin *et al.*, "In vivo treatment of mice with heat shock protein, gp96, improves survival of skin grafts with minor and major antigenic disparity," *Transplant Immunol.* 3:179-85 (2006)("the 2006 paper"), submitted herewith as Reference CV of Applicants' Supplemental Information Disclosure Statement). The 2006 paper demonstrates the immunosuppressive properties of gp96 isolated from liver

in a skin graft model using two 100 microgram doses of gp96 administered subcutaneously after transplant. The 2006 paper explicitly addresses the source issue at page 184, column 1, stating that gp96 isolated from liver, skin, and MethA induced tumors was equally effective at prolonging graft survival regardless of the source from which it was purified. The 2006 paper further states that this finding is in agreement with their previous work showing that "gp96-mediated downregulation of immune responses was independent of the tissue type from which the protein was obtained" (page 184, col. 1, para. 3, citing the 1999 paper and the 2004 paper). In summary, Applicants submit that a fair reading of the three Chandawarkar papers, giving due deference to the scientists' own interpretation of their results as published in a peer-reviewed journal article, demonstrates the correctness of Applicants' position that the tissue source of the hsp is irrelevant to its immunosuppressive activity.

With respect to the Examiner's contention that the most likely conclusion to be drawn from the data in Experiment 2 of the specification is that the gp96 must derive from the same genetic source as the graft, Applicants maintain their position as stated in their November 25, 2004 response. Briefly, Applicants note that the only dose of rat liver gp96 administered was a low dose of 10 micrograms, which amount was less immunosuppressive than a higher dose in certain experiments; that is, as assayed on certain days, both the rat and mouse liver gp96 were less effective at the 10 microgram dose than a higher dose for enhancing the survival of skin grafts in mice (see the specification at pages 40-41 and Figures 2A-2E). Applicants submit that the rat data in Experiment 2 is not inconsistent with what has been shown by the Chandawarkar *et al.* references, namely that the tissue source of the hsp is irrelevant to its immunosuppressive activity.

Enablement: time of administration of hsp

The Examiner asserts that the 2004 Chandawarkar paper demonstrates that the cell, tissue, or organ graft antigens must be administered before the suppressive dose of gp96, and that Applicants' specification does not address this issue. Applicants agree that the three Chandawarkar papers each teach that the immunosuppressive dose of hsp is effective only against an active, ongoing immune response and that therefore, the hsp must be administered after the onset of the immune response intended to be suppressed (see *e.g.*, the 2004 paper at page 621, col 1, para. 2, concluding that "suppression of the immune response by high-dose gp96 requires an ongoing immune response as a substrate"). Applicants point out that the requisite immune response is present where the hsp is administered after transplantation (as

in the 2004 and 2006 papers), or where the hsp is administered after an immune response is elicited by pretreatment with graft-derived antigen (*e.g.*, as in the experiment with Meth A derived gp96 shown in Figure 3B of the 1999 paper).

In response to the Examiner's objection, Applicants submit that the specification expressly contemplates the administration of the suppressive dose of hsp at times after the onset of the immune response intended to be suppressed. See, for example, the specification at page 36, lines 26-36, which states:

> Suppression of a rejection response may also be enhanced by administration of the hsp after transplantation. Transplantation may trigger an incipient graft rejection response. Administration of hsp after transplantation may specifically suppress such an activated rejection response.
>
> In a specific embodiment, the treatment regimens provided herein comprise administration of the hsps after the onset of the graft rejection response; i.e., after the specific immune response has already developed.

Thus, the specification expressly provides for administration of the hsp after transplantation of the graft. The specification also specifically provides for administration of the hsp before transplantation but after an immune response against donor-derived alloantigen has been elicited. See, for example, page 37, lines 13-35, of the specification which teaches that the recipient may be pre-treated with a sample of donor tissue prior to the administration of the immunosuppressive dose of hsp, which then operates to suppress the recipient's immune response against donor alloantigens before the graft is transplanted. In summary, Applicants submit that the specification expressly contemplates the administration of immunosuppressive doses of hsp at the times demonstrated to be effective by the Chandawarkar papers, *i.e.*, after a specific immune response against the graft has already developed, elicited either by the graft itself or by pretreatment with donor tissue. Applicants point out that new claims 54 and 55 specifically recite the administration of the immunosuppressive dose of hsp at these times.

In view of the preceding remarks, Applicants submit that new claims 54-69 satisfy the enablement requirements of 35 U.S.C. §112, first paragraph, and respectfully request that this rejection be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description, Should be Withdrawn

The Examiner rejected claim 53 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that claim 53 added new matter because the specification at pages 7 and 9 supports only a method wherein the heat shock protein is not an alloantigen of the *grafted tissue*, as opposed to the *grafted cells, tissue, or organ*, recited by claim 53.

Applicants note that claim 53 has been canceled, but address the Examiner's rejection as it may apply to new claim 58. In response, Applicants submit that the method of new claim 58 is expressly supported by the claims as originally filed in this application. See, for example, original claim 2 at page 42 of the specification which recites "[t]he method of claim 1, wherein the heat shock protein is not an alloantigen of the grafted cells, tissue, or organ."

Applicants further note that the specification as filed fully supported the language of claim 58, *e.g.*, at page 9, line 35, and in the teachings throughout, such as at page 11, lines 24-27. Applicants point out that the subject matter of a claim need not be described literally, *in haec verba*, in order for the disclosure to satisfy the written description requirements of 35 U.S.C. §112, first paragraph. See M.P.E.P. § 2163.02 (page 2100-185 of 8th ed. Rev. 3 Aug. 2005). Nevertheless, Applicants have amended the specification to incorporate the language of original claim 2. See M.P.E.P. § 2163.06 (page 2100-190 of 8th ed. Rev. 3 Aug. 2005)(citing *In re Benno*, 768 F.2d 1340 (Fed. Cir. 1985) which provides that, since the claims as filed in the original specification are part of the disclosure, the Applicant may amend the specification to include the subject matter of an originally filed claim.

In view of this express support in the specification as originally filed, Applicants respectfully request that the Examiner withdraw this rejection.

The Rejection Under 35 U.S.C. § 102(b) Should be Withdrawn

The Examiner rejected claims 33, 35, 38, 40, 44, and 50 under 35 U.S.C. §102(b) as allegedly anticipated by Srivastava *et al.*, "Tumor rejection antigens of chemically induced sarcomas of inbred mice," *Proc. Natl. Acad. Sci. U.S.A.* 83:3407-3411 (1986).

In response, Applicants note that claims 33, 35, 38, 40, 44, and 50 have been canceled, rendering the rejection moot with respect to those claims. Nevertheless, Applicants address the rejection with respect to new independent claims 54-56.

In order to anticipate the claimed invention, a single reference must teach each and every element of the claims. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628 (Fed. Cir. 1987).

Srivastava *et al.* (1986) teaches that cytosol and membrane preparation derived from MethA induced tumors growing in mice contain tumor rejection antigens ("TRAs") such that immunization of mice with the cytosolic or membrane preparations was effective to protect the mice against subsequent challenge with live Meth A tumor cells. Srivastava also teaches that the observed tumor immunity was only effective within a limited dosage range and that higher doses caused enhancement of tumor growth (see Figure 5 and accompanying discussion). The method taught by Srivastava comprises administering the cytosolic or membrane preparations before challenge with live Meth A tumor cells.

New claims 54, 55, and 56, each recite a method of inhibiting rejection of grafted cells, tissue, or organ in a mammal *in need thereof* comprising administering *to the mammal* a dose, effective to inhibit graft rejection, of a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, *wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ*, wherein the heat shock protein is a member of the hsp90 family of heat shock proteins.

Applicants submit that Srivastava *et al.* (1986) does not anticipate the claimed methods because the preparations administered by Srivastava necessarily comprised peptides that were alloantigens of the grafted Meth A tumors, since the preparations were either membrane or cytosolic protein fractions obtained from Meth A tumor cells growing in mice.

In addition, Applicants submit that the requirement in the claims of administration to a mammal in need of inhibiting a graft rejection provides novelty over the method of Srivastava *et al.* (1986), in which the mammals (the mice) are not in need of inhibiting rejection of the grafted Meth A sarcoma cells, but rather are in need of promoting such rejection of the tumor cells.

In view of the above remarks, Applicants submit that new claims 54-69 satisfy the requirements of 35 U.S.C. §102(b) and respectfully request that this rejection be withdrawn.

Conclusion

Applicants believe that the present claims meet all of the requirements for patentability. An early allowance of the application is earnestly requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

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